UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,470	11/20/2001	Ruey S. Liou	TNX99-05-01	3795

26839 7590 03/27/2003

TANOX, INC.
10301 STELLA LINK
HOUSTON, TX 77025

EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/991,470	Liou
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 17-23 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 17-23 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's pre-amendment received on 9/13/02 has been entered. Applicant's request for the cancellation of claims 1-27 and addition of new claims 28-34 is acknowledged. However, only claims 1-16 were present in the application as filed. As such the office has canceled claims 1-16 and **renumbered new claims 28-34 as claims 17-23** according to Rule 1.126. Claims 17-23 are therefore pending in the instant application. Please note that any subsequent amendments to the pending claims should refer to claims 17-23. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to carrying out his invention.

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of inhibiting the binding of IgE to the high affinity IgE receptor using the disclosed vectors encoding an antibody which does not bind to IgE bound to the high or low affinity IgE receptors, but which inhibits the binding of IgE to both the high and low affinity IgE receptors, does not reasonably provide enablement for the use of any vector and

promoter to express the disclosed antibodies in order to inhibit IgE or suppress IgE-mediated allergic disease *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification teaches nucleic acids, vectors, and host cells which encode and/or express an antibody which does not bind to IgE bound to the high or low affinity IgE receptors, but which inhibits the binding of IgE to both the high and low affinity IgE receptors. The specification further discloses the use of said nucleic acids, vectors, and cells to treat allergic disease by expressing the disclosed anti-IgE antibodies *in vivo*.

The specification does not provide an enabling disclosure for treating any and all allergic diseases by administering any vector encoding any anti-IgE antibody which inhibits binding of IgE to high affinity IgE receptors and which does not bind to IgE bound to an IgE receptor. The specification discloses the transfection of cells *in vitro* or *in vivo* with a vector encoding an anti-

an *in vitro* working example which teaches the construction of an adenovirus encoding Hu-901, and *in vivo* working example which demonstrates that intravenous injection of transgenic mice which express an IgE antibody that contains a human constant epsilon region with an adenovirus encoding Hu-901 results in a transient decrease in serum IgE. The specification does not provide sufficient guidance as to other vector/promoter combinations, other routes of administration, and other anti-IgE antibodies which would demonstrate a similar inhibition of IgE in the transgenic

mice or in humans. Further, the specification does not correlate the level of Hu-901 expression and the level of temporary IgE suppression observed with any therapeutic effect on any allergic condition or disease.

At the time of filing, the art did not consider the delivery and expression of therapeutic genes using nucleic acid expressions systems including adenoviruses to be predictable. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2).Verma points out that, " [t]here are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression", that, " [a] critical limitation of retroviral vectors is their inability to infect non-dividing cells, such as those that make up muscle, brain, lung, and liver tissue " (Verma et al. (1997) Nature, Vol. 389, page 240, column 1, paragraph 3,

enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than

the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2,). Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression using nucleic acid vectors, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic levels of an anti-IgE antibody as discussed above, the lack of correlation between the level of Hu-901 expression and the level and duration of IgE suppression observed in the applicant's working example and any therapeutic

experimentation to practice the invention as claimed and the skilled artisan would not have predicted success in treating allergic diseases using the nucleic acids of the instant invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recites methods of inhibiting the binding of IgE to the high-affinity IgE receptor, methods of inducing a host cell to express an anti-IgE antibody, and methods of suppressing an IgE-mediated allergic disease comprising administering a vector. However, the claims fail to identify the target of the administration step. As such, it is unclear whether the claims encompass both in vitro and in vivo methods. In particular, it is unclear whether the host cells are in vitro or in vivo, and whether the inhibition of IgE binding occurs in vitro or in vivo. Thus, the metes and bounds of the claim are confusing, rendering the claims indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

A person shall be entitled to a patent unless --

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,066,718 (5/23/00), hereafter referred to as Hardman et al.. The applicant claims methods of inducing a host cell to express an anti-IgE antibody that inhibits binding of human IgE to the high affinity IgE receptor, and methods for inhibiting the binding of IgE to its high-affinity IgE receptor. The applicant further claims said methods wherein the antibody is an scFV antibody, or wherein the antibody is Hu901 or an scFV of Hu901.

Hardman et al. teaches nucleic acids encoding the heavy and light chains of a humanized reshaped monoclonal antibody against IgE based on the TES-C21 antibody, which does not bind to either the high or low affinity receptors and further inhibits the binding of IgE to the IgE receptor (columns 23-31). Hardman et al. also teaches vectors encoding said nucleic acids, host cells transformed with said vectors, and methods of producing an anti-IgE antibody by culturing a host cell transformed by said expression vectors (Hardman et al., columns 69-70, claims 1-10). In particular, Hardman et al. teaches that the vectors encoding the anti-IgE antibody utilize strong

al., column 15, lines 22-41, and column 16, lines 18-28). Hardman et al. further teaches nucleic acids encoding single chain antibodies, scFv, encoding the heavy and light chains of a humanized reshaped monoclonal antibody against IgE based on the TES-C21 antibody, which does not bind to either the high or low affinity receptors and further inhibits the binding of IgE to the IgE receptor (Hardman et al., column 6, lines 8-15, column10, lines 28-35, and column 12, lines 29-41). Hardman et al. also appears to teach an antibody that is equivalent to what the specification

refers to as Hu-901. The specification states on page 7 that Hu-901 is described in AU 675449. The AU 675449 patent is in the same patent family as U.S. Patent 6,066,718 and has a similar disclosure. Thus, in the absence of evidence to the contrary, Hardman et al. teaches the Hu-901 antibody and the nucleic acid sequences encoding the Hu-901 antibody. Finally, Hardman et al. teaches that antibodies produced by the transfected cells can inhibiting IgE (Hardman et al., column 22, lines 15-25, and 63-67). Thus, by teaching all the limitations of the claims as written, Hardman et al. anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person
>
> manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over by U.S. Patent No. 6,066,718 (5/23/00), hereafter referred to as Hardman et al., in view of U.S. Patent No. 6,468,547 (10/22/02), hereafter referred to as Buchsbaum et al. The applicant claims methods for inhibiting the binding of IgE to its high-affinity IgE receptor comprising administering a composition comprising a vector comprising a nucleic acid encoding an anti-IgE antibody, wherein the vector is an adenoviral vector with a human CMV promoter for expression of the antibody.

Hardman et al. teaches nucleic acids encoding the heavy and light chains of a humanized reshaped monoclonal antibody against IgE based on the TES-C21 antibody, which does not bind to either the high or low affinity receptors and further inhibits the binding of IgE to the IgE

cells transformed with said vectors, and methods of producing an anti-IgE antibody by culturing a host cell transformed by said expression vectors (Hardman et al., columns 69-70, claims 1-10). In particular, Hardman et al. teaches that the vectors encoding the anti-IgE antibody utilize strong promoters, and in particular the CMV promoter, to express the encoded antibody (Hardman et al., column 15, lines 22-41, and column 16, lines 18-28). Hardman et al. also teaches the use of the disclosed antibodies to inhibit IgE (Hardman et al., column 22, lines 15-25, and 63-67).

Hardman et al., while teaching the use of vectors encoding an anti-IgE antibody operatively linked to the human CMV promoter, differs from the instant invention by failing to specifically teach the use of an adenoviral vector. Buchsbaum et al. supplements Hardman et al. by teaching the use of adenoviral vectors to express single chain antibodies under transcriptional control of the CMV promoter, e.g. Ad21 (Buchsbaum et al., column 17, lines 14-19). Buchsbaum et al. further provides motivation for using an adenoviral vector to express an antibody or single chain antibody over plasmid vectors by teaching that the adenoviral vector encoding the antibody exhibited the highest in situ gene transfer of the tested vectors (Buchsbaum et al., column 23, lines 57-59). Thus, in view of the superiority of adenoviral vectors over plasmid vectors as taught by Buchsbaum et al., it would have been *prima facie* obvious to the skilled artisan to substitute and adenoviral vector for the plasmid vector taught by Hardman et al. Further, in view of the teachings of Buchsbaum et al. that adenoviruses encoding an antibody can successfully express the encoded antibody in host cells, the skilled artisan would have had a reasonable expectation of

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's

supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER